

Changes of blood PACAP level in patients with Parkinson's disease

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Introduction: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide with antiapoptotic, antioxidant, regulatory and antiinflammatory effects proved by numerous *in vitro* and *in vivo* studies. In the last few years several studies examined changes of PACAP levels in human samples to show alterations in various physiological and pathological conditions. Plasma PACAP concentrations were significantly increased after acute spontaneous basal ganglia hemorrhage and reduced in the cerebrospinal fluid (CSF) of Alzheimer's disease patients. We showed correlation between patient mortality and PACAP levels in severe traumatic brain injury. Earlier experiments did not show changes of PACAP levels in the CSF of Parkinson's disease (PD) patients. Our aim was to examine the PACAP in blood samples of patients with PD (n=107, control=39).

Methods: We measured the plasma PACAP38 level of PD patients with sandwich-type ELISA and searched for correlations with clinical parameters such as gender, age, stage and subtype of disease, type of treatment and specified scores for PD [Hoehn-Yahr, Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)].

Results: We showed significantly decreased PACAP38 levels in PD patients over 50 compared to younger group and in Hoehn-Yahr scale stage 3 compared to HYS2 group. Elevated levels were found after deep brain stimulation. We didn't find significant correlations between plasma PACAP38 levels and the MDS-UPDRS or the type of pharmacological treatment.

Conclusion: Earlier experiments did not find significant changes in CSF PACAP levels of PD patients, however, our experiments showed decreased level in plasma samples. The reduced levels of PACAP found in PD patients and the significant increase after DBS treatment confirm the hypothesis that the neuroprotective effect of PACAP could have a role in PD. Based on our results we assume the possibility of using PACAP as a biomarker to monitor the course of the disease.

Keywords: Parkinson's disease, PACAP

CHANGES OF BLOOD PACAP LEVEL IN PATIENTS WITH PARKINSON'S DISEASE

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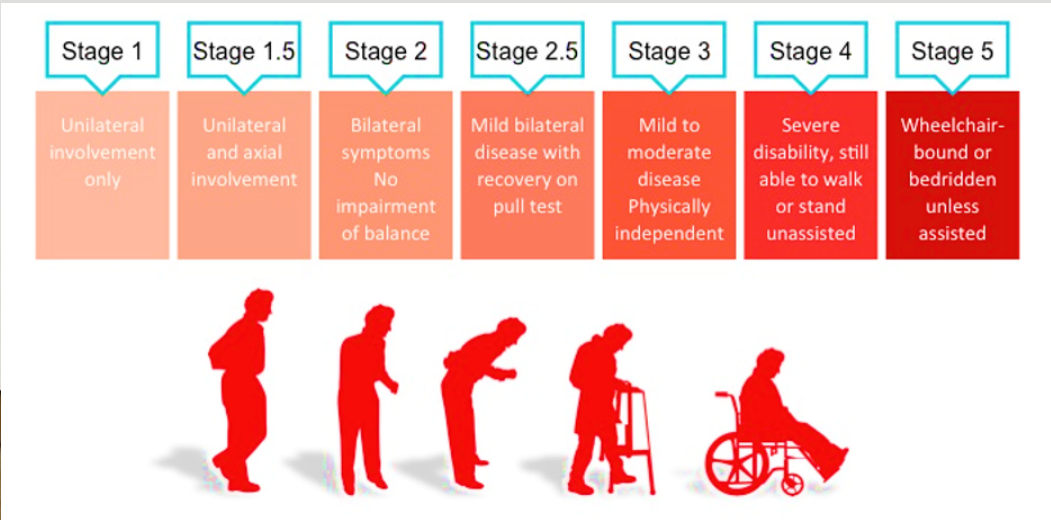
Introduction

- Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide with several antiapoptotic, antioxidant, regulatory and antiinflammatory effects proved by numerous *in vitro* and *in vivo* studies.
- In the last few years, several studies examined changes of PACAP level in human samples to show alterations in various physiological and pathological conditions including the following in the field of neurology:
- Significantly increased plasma PACAP concentrations were present after acute spontaneous basal ganglia or subarachnoidal hemorrhage, traumatic brain injury and also in migraine.
- Reduced PACAP levels were found in Alzheimer's disease patients in several brain areas and in the cerebrospinal fluid (CSF).
- Reduced PACAP levels were found in multiple sclerosis in the CSF.
- Earlier experiments did not show significant changes of PACAP levels in CSF in the case of patients with Parkinson's disease (PD).
- We proved in several PD animal models the neuroprotective effect of PACAP on dopaminerg cells that suggests its important role in the patomechanism of this disease.
- Based on these results our aim was to examine PACAP in plasma samples of patients with Parkinson's disease.

Methods

We measured plasma PACAP-38 level of PD patients and searched for correlations with clinical properties such as gender, age, stage and subtype of disease [based on the Hoehn and Yahr scale (HYS), Fig.1], type of treatment [pharmacological or deep brain stimulation (DBS)] and specified scores for PD [e.g. Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), evaluating non-motor and motor experiences of daily living and motor complications].

Sandwich-type ELISA (Myobiosource) was used to measure the PACAP-38 level of plasma samples (PD patients=107, control=39).



scale for measuring the severity of PD symptoms, classifies patients in five stages.
<http://gepezz.info/similar/5-stages-of-parkinsons-healthline.html>

Results

We showed:

- significantly decreased PACAP-38 levels in non-DBS patients compared to healthy controls (Fig.2)
- significantly elevated PACAP-38 levels in DBS treated patients compared to non-DBS patients (Fig.2)
- significantly decreased PACAP-38 levels in HYS3 compared to HYS2 patients (Fig.3)
- significantly decreased PACAP-38 levels in PD patients over 50 years compared to patients younger than 50 years (Fig.4)
- no significant correlation between plasma PACAP-38 levels and MDS-UPDRS or the type of pharmacological treatment. (Fig.5)

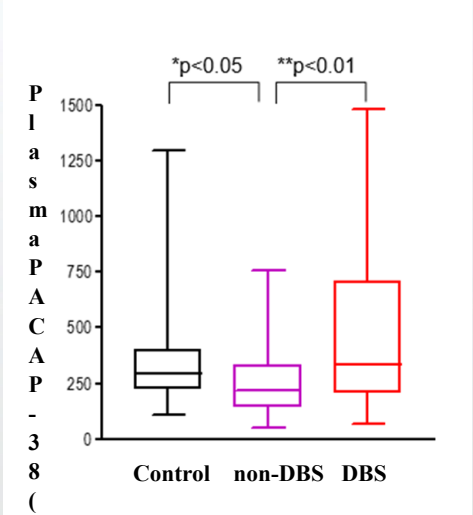


Figure. 2 PACAP-38 levels in healthy population (control), non-DBS and DBS-treated PD patients.

Significantly lower PACAP-38 levels were present ($p<0.05$) in the plasma samples of non-DBS treated PD patients in comparison to healthy control individuals. In DBS treated patients PACAP-38 levels were significantly elevated ($p<0.01$) in the plasma of PD individuals when compared to non-DBS treated patients.

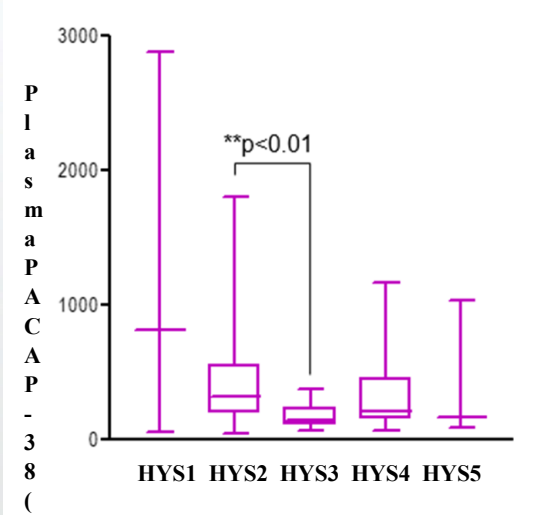


Figure. 3 PACAP-38 levels in different stages of PD.

Five subgroups were made according to the HYS: HYS1 ($n=4$), HYS2 ($n=60$), HYS3 ($n=16$), HYS4 ($n=19$) HYS5 ($n=3$). The analysis revealed a progression-dependent negative correlation between plasma PACAP-38 levels and the stages of PD. PACAP-38 levels decreased firmly until HYS3, thereafter remained steady. The differences were significant ($p<0.01$) between the HYS2 and HYS3 stages.

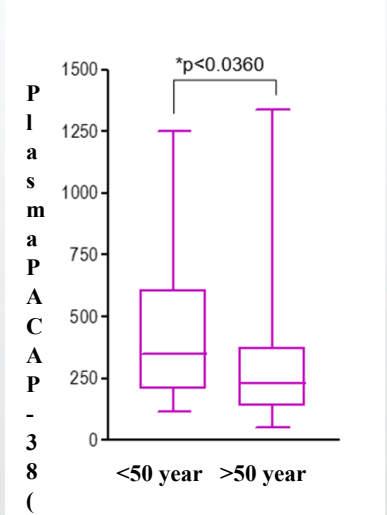


Figure. 4 Age-dependent differences of PACAP-38 levels in PD.

Plasma concentration of PACAP-38 was significantly lower ($p<0.0360$) when the age at diagnosis of PD was more than 50 years in comparison to the younger (age <50 years) group.

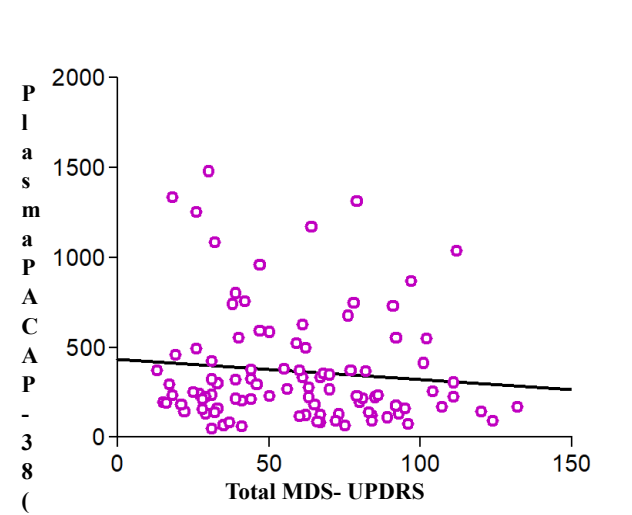


Figure. 5 PACAP-38 levels and total points of MDS-UPDRS.

Comparing ELISA results with the MDS-UPDRS score did not reveal significant correlation between plasma PACAP-38 levels and total MDS-UPDRS scores but showed a weak negative tendency.

Conclusion

- Earlier experiments did not find significant changes in CSF PACAP levels of PD patients, however, our experiments showed **decreased level** in plasma samples. The lowest PACAP levels were measured in **HYS3** and in **older ages**.
- The reduced levels of PACAP found in PD patients and the significant **increase** after **DBS treatment** confirm the hypothesis that the neuroprotective effect of PACAP could have a role in this disease. The exact origin of increased PACAP levels in DBS treated patients is yet unknown, we propose further examinations to reveal the exact patomechanism.
- Based on our results we suppose the possibility of using PACAP as a **biomarker** to monitor the course of the disease and foretell the prognosis of this neurodegenerative disorder.

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